REMARKS

Claim Status

Claims 72-76, 91 and 96 are pending in the instant application. Claims 1-71, 87-90, and 92-95 were previously canceled. Claims 77-86 were previously withdrawn. Claims 73-76, 91, and 96 were previously presented. Claim 72 was currently amended to replace the word substantial with the word significant. No new matter was entered in this amendment.

I. Rejection of Claims 72-76, 91 and 96 under 35 U.S.C. 112, second paragraph

The Office has stated that Claims 72-76, 91, and 96 are rejected under 35 U.S.C.112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. According to the Office, the term "substantial" in claim 72 is a relative term which renders the claim indefinite. In response to this rejection, the Applicants have amended Claim 72 by replacing the word "substantial" with "significant". Support for this amendment can be found on page 24:

> In fact, a significant difference was only observed at day 21, when angiotensin II-infused, vehicle treated rats demonstrated higher urinary Na^+/K^+ ratio than eplerenone-treated animals indicating that, under these experimental conditions eplerenone did not produce a significant diuretic or natriuretic effect.

The Applicants also point out that one skilled in the art would be capable of understanding the phrase, "under these experimental conditions eplerenone did not produce a significant diuretic or natriuretic effect", to mean that the diuretic effects of the eplerenone-experimental animals did not differ significantly from the diuretic effects of the control animals.

Claims 73-76 all depend from Claim 72 and therefore, following the amendment of Claim 72, the rejection of Claims 73-76 is now moot.

II. Rejection of Claims 72-76, 91 and 96 under 35 U.S.C. 102(b)

Applicants assert that the claims, as amended, contain limitations that are not present in either Grob et al, or Thosar et al.

Neither Grob et al. nor Thosar et al. teach or suggest a dose of epoxy-steroidal aldosterone antagonist in an amount "that produces no significant diuretic or anti-hypertensive effect in the subject," as presently amended claim 72 now requires. All of the pending claims depend from claim 72, and therefore, none of the pending claims are anticipated by either Grob et al. or Thosar et al.

Please note that Grob et al. discloses dosage units of 5-150 mg, *only* when combined with a second, diuretic compound. Grob states at Column 15, lines 10-17:

> As a special form of these pharmaceutical compositions and medicaments according to the invention there come into consideration also those which contain, **in addition to** the aldosterone-antagonistic compound of the formula I (including salts) according to the invention, **which is referred to as component A** in this context, **also a diuretic component B which is non-specific with regard to electrolytes**. (emphasis added)

Grob et al, goes on to state, at Column 15, lines 63-68 to Column 16, lines 1-16:

> For example, **such combination preparations** contain, per dosage unit, from 5 to 150 mg, especially from 10 to 50 mg, of **a compound of the formula I** or a salt thereof **as component A** and, as component B, for example from 10 to 100 mg, especially from 25 to 50 mg, of 2-chloro-5- [3-hydroxy-1-oxo-isoindolyl-(3)]-benzenesulphonamide or 4-(2-methylenebutyryl)-2,3-dichlorophenoxyacetic acid, from 5 to 50 mg, especially from 12 to 25 mg, of 6-chloro-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide or 2-chloro-4-furfurylamino-5-carboxybenzenesulphonamide, from 2 to 20 mg, especially from 5 to 10 mg, of 2-phenoxy-3- 3-(1-pyrrolyl)-propyl!-5-carboxybenzenesulphonamide, from 0.1 to 1.0 mg, especially from 0.25 to 0.5 mg, of 3- cyclopentylmethyl-6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide or 2-phenoxy-3-butylamino-5-carboxybenzenesulphonamide, from 100 to 400 mg, especially 200 mg, of 4- thenoyl-2,3-dichlorophenoxyacetic acid and from 5 to 25 mg, especially 10 mg, of racemic (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)-acetic acid, or half the amount of the laevo-form of this acid. (emphasis added).

Thus, it can be seen that Grob et al. does not fairly enable the use of an epoxy-steroidal compound in an amount "that produces no significant diuretic or anti-hypertensive effect in the subject," as presently amended claim 72 now requires. Also note that claims 91 and 96, which contain the limitation of administration of from about 0.5 to about 10 mg, further carry the limitation of administering an epoxy-steroidal compound in an amount "that produces no substantial diuretic or anti-hypertensive effect in the subject," since both claims 91 and 92 depend from Claim 72.

Finally, neither Grob et al. nor Thosar et al. are enabling for a method that includes administering an amount of an epoxysteroidal aldosterone antagonist to a subject in an amount that produces substantially no diuretic or anti-hypertensive effect. While both references describe a broad range of dosages, "An invitation to investigate is not an inherent disclosure." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 2004 U.S. App. LEXIS 11248, *31, Docket 03-1120, Fed. Cir. 2004). Since neither Grob et al., nor Thosar et al. describe the limitations present in the claims, as amended, the claims are not anticipated.

III. Claim rejections Under 35 U.S.C. § 103

Claims 72-76 and 87-96 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grob et al. in view of MacLaughlan et al. (WO 96/24358); and over Thosar et al.

A. The Claims, as Amended, are not Obvious

None of the references of record teach or suggest the limitation of administering an amount of an epoxysteroidal aldosterone antagonist to a subject in an amount that produces substantially no diuretic or anti-hypertensive effect, as the presently amended claims require. MacLaughlan et al. teaches administering spironolactone at a low dose to reduce or avoid side effects of spironolactone. (See WO 96/24358, page 1, lines 1-13.)

Grob et al. states, at Column 3, lines 48-62:

> 20-Spiroxane derivatives having an aldosterone-antagonistic action are known, cf., for example, Fieser and Fieser: Steroids; page 708 (Reinhold

> Publ. Corp., New York, 1959) and British Patent Specification No. 1,041,534; also known are analogously active 17β- □ydroxyl-21-carboxylic acids and their salts, cf., for example, U.S. Pat. No. 3,849,404. Compounds of this kind that have hitherto been used in therapy, however, have a considerable disadvantage in that they always possess a certain sexual-specific activity which has troublesome consequences sooner or later in the customary long-term therapy. Especially undesirable are the troublesome effects that can be attributed to the anti-androgenic activity of the known anti-aldosterone preparations.

Grob further states, at Column 3 lines 63-68 to Column 4, line 1:

> It has now been found that the above-characterised 9α,11α-epoxy compounds of the formula I surprisingly exhibit these undesirable side-effects to a substantially lesser degree although they completely retain the favourable anti-aldosterone action of compounds that have an analogous structure but that are not substituted in the 9, 11-position.

Therefore, one skilled in the art would not be motivated to combine the teachings of Grob et al. with the teachings of MacLaughlan et al., since the lower dosage taught in MacLaughlan et al. would apparently not be necessary when administering the compounds of Grob et al.

Further, MacLaughlan et al. teaches that there are several underlying causes of Heart Failure, such as hypertension or cardiomyopathy (See page 1, lines 17-21). Applicants believe that administering an epoxy-steroidal aldosterone antagonist in an amount that produces substantially no diuretic or anti-hypertensive effect would not be made obvious considering this teaching.

Thosar et al. does not teach or suggest administering an epoxy-steroidal aldosterone antagonist in an amount that produces substantially no diuretic or anti-hypertensive effect, nor does it teach treatment or prevention of myocardial infarction.

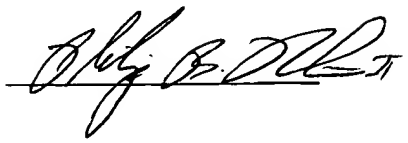
Therefore, it is believed that Thosar et al., alone or in combination with any other reference, does not render the instant claims obvious.

IV. Conclusion

If a telephonic interview with Applicant's representative would aid in the prosecution of this application, the Examiner is cordially invited to contact

Applicant's representative at the below listed number.

Respectfully submitted,



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